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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/869,629

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Peter Knox

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EXAMINER

LAM, ANN Y

ART UNIT

PAPER NUMBER

1641

DATE MAILED: 05/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/869,629	Applicant(s) KNOX ET AL.	
	Examiner Ann Y. Lam	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 March 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6,8-15,20,24-27,30 and 31 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6,8-15,20,24-27,30 and 31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Claims

Claims 7, 16-19, 21-23, 28 and 29 are cancelled.

Claims 1-6, 8-15, 20, 24-27, 30 and 31 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "high" in claim 30 is a relative term which renders the claim indefinite. The term "high" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 1-6, 8-9, 11-15, 20, 27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Buck et al., "Photochemically induced dynamic nuclear polarization investigation of complex formation of the NH₂-terminal DNA-binding domain of *lac* repressor with poly[d(AT)]", Biochemistry, Vol. 77, No. 9, pp.5145-5148.

Yu discloses performing an assay on a biological species using an assay reagent (col. 40, lines 37-38) containing at least one NMR active nucleus (col. 40, lines 40-45) to perform an assay, said assay reagent being introduced as an initial reagent, formed in situ during the assay or formed as a product of the assay (col. 8, lines 56-59);

and analyzing the assay reagent and/or the assay by NMR for a physical or chemical change in the biological species that is independent of the interaction of the biological species with the NMR active nucleus, ¹³C or ¹⁵N (i.e., binding between receptor and agent, column 9, lines 8-19; column 40, lines 37-45, and column 41, lines 41-48.)

Examiner notes that the step of "optionally using the NMR data obtained to generate further assay results" in subsection (d) of claim 1 is only an option and thus is not a required limitation in the claims.

Although Yu teaches use of NMR spectroscopy in conjunction with an NMR active nucleus to analyze an assay, Yu does not teach hyperpolarization of the NMR active nucleus by dynamic nuclear polarization. However, Buck et al. this limitation.

Buck et al. teach that the disclosed photo-chemically induced dynamic nuclear polarization increases the NMR signal intensities of a binding assay method (see page 5145, see abstract and see right column, first full paragraph). (The section on materials and methods used, on page 5145, disclosed by Buck et al. shows that the reagents are in solution form and thus, the assay is considered to be a liquid state assay method, as claimed by Applicant).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize dynamic nuclear polarization as taught by Buck et al. in the assay taught by Yu because Buck et al. teach that the dynamic nuclear polarization provides the benefit of enhancement in NMR signal intensities, such as the NMR signals in the Yu method.

As to the following claims, Yu teaches the limitations as follows.

As to claims 2 and 3, the NMR active nucleus is ^{13}C or ^{15}N (col. 40, line 45.)

As to claims 4 and 5, the assay reagent is a compound which contains an artificially high concentration of an NMR active nucleus, (i.e., the NMR active nucleus added as a label to a reagent is considered to be artificially high concentration; col. 8, lines 57-58, and col. 40, lines 40-45.) As to claim 5, since the limitation "in 1-10 defined positions" is vague and indefinite (see above), the concentration of the NMR active nucleus in the Yu disclosure is considered to be in the 1-10 defined positions.

As to claim 6, the assay reagent is an organic compound comprising one or more NMR active nuclei associated with a bond which is broken during the course of the assay (i.e., the competitive displacement assay in col. 55, lines 54-56.)

As to claim 8, the analyzing step is repeated to generate information about a change with time of the assay reagent (i.e., a before and after detection.)

As to claim 9, the assay reagent is a polypeptide or protein (col. 8 lines 45-59.)

As to claim 11, the assay is a binding assay, (column 8, lines 45-59, or column 9, lines 8-19.)

As to claim 12, the assay reagent is a compound labeled with at least one NMR active nucleus (col. 40, lines 37-45.)

As to claim 13, the assay is a binding study using micro-organisms or cultured cells, (column 38, lines 9-12.)

As to claim 27, Yu also teaches that the analyzing step is performed in an aerosol or flow-through device applied to aerosol droplets where the container is used to contain the assay reagent (col. 42, lines 11-20).

As to claims 14 and 15, Yu does not teach that the hyperpolarization transfer is repeated to enhance the signal-to-noise ratio (see claim 14); the shortening effect as expressed by the improvement of signal-to-noise per unit time is a factor of 10 or more compared to known assay techniques without hyperpolarization (see claim 15). However, Buck et al. teach repeating an experiment (see page 5147, notes on figure 4). Also, the NMR analysis step in the Buck et al. reference is not disclosed as being performed in a separate container. It would have been obvious to repeat the analysis

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steps, and to perform the NMR analysis step in the same container as the hyperpolarization transfer is carried out, since it is generally recognized that repeating known steps to obtain further data, or to perform NMR analysis step in the same container as the hyperpolarization transfer is carried out involves ordinary skill, and Buck et al. teach repeating the NMR analysis and Buck et al. do not disclose that the analysis step must be performed in a separate container.

As to claim 20, Yu does not teach that the hyperpolarization transfer is carried out at a temperature of 4.2 K or less in the presence of a magnetic field of at least 1T. However, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art (*In re Aller*, 105 USPQ 233), and in this case, the temperature as claimed by Applicant is an optimum or workable range.

As to claim 30, the assay reagent is considered to contain an artificially high concentration of the NMR active nucleus

3. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Buck et al., "Photochemically induced dynamic nuclear polarization investigation of complex formation of the NH₂-terminal DNA-binding domain of *lac* repressor with poly[d(AT)], and further in view of Katahira et al., "NMR studies of G:A mismatches in oligodeoxyribonucleotide duplexes modeled after ribozymes", *Nucleic Acids Research*, 1993, Vol.21, No. 23, pp. 5418-5424.

Yu in view of Buck et al. teach the invention substantially as claimed (see above with respect to claim 1). More specifically, as to claim 10, Yu et al. teach that the assay using NMR technique is a nucleic acid hybridization assay (see column 8, lines 60-67.) Moreover, while Buck et al. teach that photochemically induced dynamic nuclear polarization (i.e., photo-CIDNP) increases the NMR signal intensities of an assay method (see page 5145, see abstract and see right column, first full paragraph), Buck et al. do not teach that the assay is a hybridization assay. Rather Buck et al. teach that the assay relates to the binding between a protein and an oligonucleotide (see abstract on page 5145). Buck et al. is silent as to whether dynamic nuclear polarization can be utilized in a hybridization assay. However, Katahira et al. teach this limitation.

Katahira et al. teach that photochemically induced dynamic nuclear polarization (i.e., photo-CIDNP) in an NMR method can be used to study base pairing, i.e., hybridization (see page 5422, left column, third full paragraph, disclosing that the testing was done in solution form). It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize photochemically induced dynamic nuclear polarization as taught by Katahira et al. to study a hybridization assay, such as the hybridization assay disclosed by Yu. One of ordinary skill in the art would have reasonable expectation of success because Buck et al. teach that photochemically induced dynamic nuclear polarization provides the benefit of enhancing NMR signals in an assay method, and Katahira et al. specifically teaches that the NMR detection using dynamic nuclear polarization can be used to detect base pairing, i.e., hybridization, such as the hybridization assay disclosed by Yu.

4. Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Buck et al., "Photochemically induced dynamic nuclear polarization investigation of complex formation of the NH₂-terminal DNA-binding domain of *lac* repressor with poly[d(AT)]", Biochemistry, Vol. 77, No. 9, pp.5145-5148, as applied to claim 1, and further in view of Obremski, 6,110,749.

Yu in view of Buck et al disclose the invention substantially as claimed (see above with respect to claim 1), except for more than one assay being multiplexed (claim 24), and for the assay being performed in a multispot assay array (claim 25).

It would have been obvious to one of ordinary skill in the art to provide a multiplexed or multispot assay as taught by Obremski using the Yu in view of Buck et al. method of analysis, as would be desirable for simultaneous assays as taught by Obremski, such simultaneous assays providing the advantage of allowing more assays to be performed quickly.

5. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Buck et al., "Photochemically induced dynamic nuclear polarization investigation of complex formation of the NH₂-terminal DNA-binding domain of *lac* repressor with poly[d(AT)]", Biochemistry, Vol. 77, No. 9, pp.5145-5148, as applied to claim 1, and further in view of Pines et al., 6,426,058

Also, as to claim 26, Yu in view of Buck et al. teach the invention substantially as claimed (see above), except for the analyzing step being performed by using both NMR

spectroscopy and magnetic resonance imaging, and repeating the examination at least once.

Pines does however teach that a sample can be analyzed using both NMR spectroscopy and magnetic resonance imaging (see column 8, lines 60-63), and that multiple parameters can be detected, and multiple techniques can be employed to collect and manipulate nuclear magnetic resonance data (col. 19, lines 3-5.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize MRI detection as taught by Pines in the method taught by Yu in view of Buck et al. because Pines teaches that NMR spectroscopy and MRI detection can both be used to analyze a sample.

6. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of , in view of Buck et al., "Photochemically induced dynamic nuclear polarization investigation of complex formation of the NH₂-terminal DNA-binding domain of *lac* repressor with poly[d(AT)]", Biochemistry, Vol. 77, No. 9, pp.5145-5148, as applied to claim 1, and further in view of Neild et al., "Uroscopy in the 21st Century: high-field NMR spectroscopy", Nephrol Dial Transplant (1997), 12: 404-417.

Yu in view of Buck et al. teach the invention substantially as claimed (see above), except for the assay reagent being an organic compound comprising two or more NMR active nuclei associated with a chemical bond which is broken during the course of the assay such that when the bond is intact, the NMR active nuclei are spin coupled and

when the bond is broken the spin coupling is disrupted. Neild et al. teach this limitation however.

Neild et al. teach that individual magnetic nuclei can interact with each other to produce additional splittings of the NMR peaks, called spin-spin or J coupling (see page 405, left column). Neild et al. teach that these interactions are also used for structural identification since they depend on molecular shapes and conformations (page 405, left column.) It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the spin coupling as taught by Neild et al. in the Yu invention because Neild teaches that such spin coupling provides the advantage of structural identification.

Response to Arguments

Applicant's arguments filed March 6, 2006, has been considered but is moot in view of the new grounds of rejection. (Buck et al. and Katahira et al. teach dynamic nuclear polarization enhancement of NMR technique, and both references teach that the methods are performed in solution.) As to the argument with respect to the rejection under 112, second paragraph, this argument is not persuasive. Applicant states that one skilled in the art would know that "an artificially high concentration of the NMR active nucleus" means the same as "an artificially-enriched abundance of the NMR active nucleus. This is not persuasive because while an artificially-enriched abundance of NMR active nucleus may mean an artificial concentration of NMR active nucleus, it may not necessarily mean an artificially *high* concentration of the NMR active nucleus.

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(It is unclear as to what is considered artificially high concentration as opposed to just artificial concentration but not necessarily high.)

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on Mon.-Fri. 10-6:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A.L.  5/15/06


LONG V. LE 05/15/06
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